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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/924,896	08/08/2001	Dennis W. Metzger	1954.1002-009	3394

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 02/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/924,896	METZGER ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *1-7,9-15,17-19,21-23 and 25-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8, 16, 20, 24 and 30-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12-10-04 has been entered.

Claims 1-45 are pending. Claims 8, 16, 20, 24 and 30-45 are under consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 16 and 36-41 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: what is compared to determine whether the immune response to a T-cell independent antigen is enhanced in a host.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 8, 16, 20, 24 and 30-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

Claims 8, 16 and 30-41 are directed to a method of inducing or enhancing an immune response to a T-cell independent (TI) antigen in a host comprising administering to the host the TI antigen and a polynucleotide encoding IL-12. Claims 20, 42 and 43 are directed to a method of inducing an immune response to *Streptococcus pneumoniae* in a host comprising administering to the host the TI antigen of *Streptococcus pneumoniae* and a polynucleotide encoding IL-12. Claims 24, 44 and 45 are directed to a method of inducing an immune response to *Neisseria meningiditis* in a host comprising administering to the host the TI antigen of *Neisseria meningiditis* and a polynucleotide encoding IL-12. Claims 30-45 specify the T-cell independent antigen as a carbohydrate antigen, lipid antigen, a carrier conjugate antigen, a lipopolysaccharide antigen, or a phage antigen, and the immune response is a humoral immune response that enhances IgG2a and UgG3 antibody response.

The specification only discloses the use of **IL-12 protein** and a TI antigen for inducing or enhancing an immune response to a TI antigen in a host. The claims encompass using a TI antigen and a polynucleotide encoding an IL-12 protein to induce or enhance an immune response to a TI antigen in a host, or using a corresponding TI antigen and polynucleotide encoding an IL-12 protein to induce an immune response to *Streptococcus pneumoniae* or *Neisseria meningiditis* in a host.

The specification fails to provide adequate guidance and evidence for how to use the polynucleotide or vector expressing IL-12 protein in combination with a TI antigen to induce or enhance an immune response to a TI antigen in a host, or to induce an immune response to

Streptococcus pneumoniae or *Neisseria meningiditis* in a host via various administration routes of said polynucleotide. The specification fails to provide adequate guidance and evidence for whether sufficient polynucleotide or vector encoding IL-12 protein would be present in target site of the host such that sufficient IL-12 protein is obtained to induce or enhance immune response to a TI antigen in a host, or to induce an immune response to *Streptococcus pneumoniae* or *Neisseria meningiditis* in a host via various administration routes of said polynucleotide.

The claims read on gene delivery by using a polynucleotide or any vector expressing IL-12 protein via various administration routes *in vivo*. The state of the art for gene therapy was unpredictable at the time of the invention. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its

secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82).

In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract).

The specification only discloses effect of co-administration of IL-12 protein and TI antigen in stimulating or enhancing immune response to the TI antigen in a host but fails to provide data regarding whether co-administration of a TI antigen and a polynucleotide or vector encoding IL-12 protein can stimulate or enhance immune response to the TI antigen in a host. Delivery of a protein in vivo to stimulate or enhance immune response is different from delivery of a polynucleotide in vivo to stimulate or enhance immune response for therapeutic effects in vivo because the proteins have been expressed in vitro, however, the polynucleotide has to be delivered to the target site and sufficient amount of protein, such as IL-12 protein, has to be expressed to stimulate or enhance immune response in vivo. As discussed above, the art of gene transfer in vivo was unpredictable at the time of the invention. On skilled in the art at the time of the invention would not known whether sufficient amount of polynucleotide or sufficient expressed protein can be present in the targeted site to stimulate or enhance immune response as compared to TI antigen alone in a host and trial and error experimentation would be required to determine the in vivo effect of co-administration of a TI antigen and a polynucleotide or vector encoding IL-12 protein.

There is no evidence of record that administration of a TI antigen and a polynucleotide or vector expressing IL-12 protein to a host via various administration routes would result in sufficient expression of IL-12 protein at target site so as to provide therapeutic effects, such as inducing or enhancing an immune response to a TI antigen, or inducing an immune response to *Streptococcus pneumoniae* or *Neisseria meningiditis*, in a host. The cited references Tahara and Jiang teach using IL-12 transfected cells to stimulate immune response in mice for anti-tumor effect. Delivery of cell in vivo to stimulate an immune response for anti-tumor effect is different from delivery of a polynucleotide in vivo to stimulate an immune response for therapeutic effects in vivo because the proteins have been expressed in the transfected cells before being released in the target site, however, the polynucleotide has to be delivered to the target site and sufficient amount of protein, such as IL-12 protein, has to be expressed to stimulate or enhance immune response in vivo. Watanabe teaches intradermal injection of naked IL-12 DNA expression plasmid and Rakhmilevich delivers gold particles coated with IL-12 DNA directly to the skin overlying and surrounding target tumor site (subcutaneous tumor) via gene gun. Kim teaches intramuscular injection of IL-12 DNA. Therefore, the prior art only teaches intradermal or intramuscular injection of IL-12 DNA into a host to stimulate cell-mediated immune response, however, none of the references teach that introduction of IL-12 DNA into a host other than intradermal or intramuscular injection can stimulate or enhance immune response, or injection of IL-12 DNA can stimulate or enhance humoral immune response in a host.

Further, Kim (exhibit C) teaches codelivery of genes for IL-12 and GM-CSF along with DNA vaccine formulation for HIV-1 antigen and codelivery of IL-12 gene results in reduction of specific antibody response, while codelivery of GM-CSF genes results in enhancement of

specific antibody response, and a dramatic increase in specific CTL response from the mice coimmunized with both HIV-1 DNA vaccine and IL-12 genes (e.g. abstract). It appears that the type and level of Ab response can vary with the combination of a DNA vaccine (DNA for HIV-1 Ag) and different expression plasmids expressing different proteins (IL-12 or GM-CSF), and codelivery of IL-12 gene and DNA vaccine results in reduction of specific Ab response but dramatic increase in specific CTL response. Okada (Exhibit F) reports that "[C]oinjection of vaccine plus an IL-12 expressing plasmid also failed to modify HIV-specific serum Ab titers" and "[C]oadministration of IL-12 expression plasmid did not modify fecal IgA Ab levels. Again, however, a strong level of anti-V3 Ab was observed when we coadministered IL-12 plus GM-CSF expression plasmids" (e.g. p. 3641, right column). It seems that co-administration of IL-12 expressing plasmid and DNA vaccine for HIV-1 does not increase or enhance humoral immune response in mice as compared to HIV-1 DNA vaccine alone.

In view of the reasons set forth above, it would be unpredictable whether codelivery of various TI antigen and a polynucleotide or a vector encoding IL-12 can stimulate or enhance immune response to TI antigen, such as humoral immune response. It also would be unpredictable whether codelivery of various TI antigen and a polynucleotide or a vector encoding IL-12 can stimulate or enhance immune response to TI antigen, such as humoral immune response, in vivo via administration routes other than intradermal and intramuscular injections, for example, oral administration, intravenous administration, or intraperitoneal injection. The specification must provide sufficient enabling disclosures for the full scope of the invention claimed but fails to do so.

In view of the unpredictability of gene delivery *in vivo* and the lack of evidence of inducing or enhancing immune response to a TI antigen or inducing immune response to *Streptococcus pneumoniae* or *Neisseria meningiditis* in a host by using a TI antigen and a polynucleotide or vector expressing IL-12 protein via various administration route, one skilled in the art at the time of the invention would not know how to use the TI antigen and a polynucleotide or vector expressing IL-12 protein to practice the claimed invention.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Applicants argue that the specificaion provides data regarding the use of IL-12 protein and TI antigen to induce or enhance immune response in mice and teaches how to make and introduce the vector expressing IL-12 into a host. Applicants further cite references Tahara et al. (exhibit A), Rakhmilevich et al. (exhibit B), Kim et al. (exhibit C), Jiang et al. (exhibit D), and Watanabe et al. (exhibit E) and argue that these references show how to administer IL-12 polynucleotide into a host and an effective amount of IL-12 protein is expressed in vivo (amendment, p. 2-3). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph rejection. The specification only discloses effect of co-administration of IL-12 protein and TI antigen in stimulating or enhancing immune response to the TI antigen in a host but fails to provide data regarding whether co-administration of a TI antigen and a polynucleotide or vector encoding IL-12 protein can stimulate or enhance immune

response to the TI antigen in a host. Delivery of a protein in vivo to stimulate or enhance immune response is different from delivery of a polynucleotide in vivo to stimulate or enhance immune response for therapeutic effects in vivo because the proteins have been expressed in vitro, however, the polynucleotide has to be delivered to the target site and sufficient amount of protein, such as IL-12 protein, has to be expressed to stimulate or enhance immune response in vivo. The prior art only teaches intradermal or intramuscular injection of IL-12 DNA into a host to stimulate cell-mediated immune response, however, none of the references teach that introduction of IL-12 DNA into a host other than intradermal or intramuscular injection can stimulate or enhance immune response, or injection of IL-12 DNA can stimulate or enhance humoral immune response in a host. It was unpredictable at the time of filing whether codelivery of various TI antigen and a polynucleotide or a vector encoding IL-12 can stimulate or enhance immune response to TI antigen, such as humoral immune response. It also was unpredictable whether codelivery of various TI antigen and a polynucleotide or a vector encoding IL-12 can stimulate or enhance immune response to TI antigen, such as humoral immune response, in vivo via administration routes other than intradermal and intramuscular injections, for example, oral administration, intravenous administration, or intraperitoneal injection.

Applicants cite Okada reference (Exhibit F) and argue that Okada show administration of a polynucleotide expressing IL-12 in combination with an HIV antigen induce immune response to the antigen (amendment, p. 4). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph rejection. Okada use the combination of a polynucleotide expressing IL-12 protein and a DNA vaccine for HIV-1, however, the present

invention is directed to the combination of a polynucletoide expressing IL-12 and a TI antigen. As discussed above, Kim (exhibit C) shows codelivery of IL-12 gene and DNA vaccine for HIV-1 results in reduction of specific antibody response, while codelivery of GM-CSF gene and said DNA vaccine results in enhancement of specific antibody response, and a dramatic increase in specific CTL response from the mice coimmunized with both HIV-1 DNA vaccine and IL-12 gene. Okada reports that "[C]oinjection of vaccine plus an IL-12 expressing plasmid also failed to modify HIV-specific serum Ab titers" and "[C]oadministration of IL-12 expression plasmid did not modify fecal IgA Ab levels. Again, however, a strong level of anti-V3 Ab was observed when we coadministered IL-12 plus GM-CSF expression plasmids" (e.g. p. 3641, right column). It seems that co-administration of IL-12 expressing plasmid and DNA vaccine for HIV-1 does not increase or enhance humoral immune response in mice as compared to HIV-1 DNA vaccine alone. It appears that gene delivery to a host to stimulate an immune response needs to be considered individually and the result of one gene delivery can not be extrapolated into success for another gene delivery in vivo. Without enabling disclosure, one skilled in the art at the time of the invention would not know whether codelivery of various TI antigen and a polynucleotide or a vector encoding IL-12 can stimulate or enhance immune response to TI antigen, such as humoral immune response, via various administration route.

Applicants argue that Deonarian, Eck and Gorecki references do not discuss IL-12 gene therapy, therefore, they are not relevant to the claimed invention, and if those references are relevant, then the teachings of Exhibits A-E would be relevant to the enablement of the claimed invention (amendment, p. 4). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph rejection and the reasons set forth above. Deonarian, Eck

and Gorecki references provide a general state of gene delivery in vivo and show that gene delivery in vivo was unpredictable at the time of the invention. Therefore, these references are relevant to the claimed invention, however, gene delivery to a host to stimulate an immune response needs to be considered individually and the result of one gene delivery can not be extrapolated into success for another gene delivery in vivo. As discussed above, the teachings of Exhibit A-E fail to provide sufficient enabling disclosure for the claimed invention.

Applicants cite Exhibit A-F and argue that the art of gene delivery of IL-12 in vivo was not unpredictable at the time of the invention and effective dose of IL-12 polynucleotide can be extrapolated from dose-response curve derived from in vitro or in animal model (amendment, p. 5). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph rejection and the reasons set forth above.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Shin-Lin Chen, Ph.D.